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Dated: April 26, 2005

Signature: Jeffrey S. Sharp

(Jeffrey S. Sharp)

Docket No.: 28911/36128
(PATENT)

AF IZW
1437

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Alison HOPKINS

Application No.: 09/485,245

Group Art Unit: 1637

Filed: March 27, 2000

Examiner: C. Wilder

For: **COMPOSITIONS COMPRISING RANDOM
MIXTURES OF OLIGONUCLEOTIDES**

BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to the Notice of Appeal submitted December 13, 2004 in connection with the Final rejection of the above-identified patent application, dated July 12, 2004, the Appellant respectfully submits the following Appeal Brief in accordance with 37 C.F.R. § 41.37. This appeal brief is timely filed as a petition for a three-month extension of time to May 13, 2005 and a check in the amount of \$1520 covering the cost of the appeal fee pursuant to 37 C.F.R. § 41.20(b) and the extension of time, is submitted herewith. If any additional fees are deemed necessary, the Commissioner is authorized to charge the additional fees to Marshall, Gerstein & Borun LLP account number 13-2855.

04/29/2005 EFLORES 00000060 09485245

01 FC:1402 500.00 OP

04/29/2005 EFLORES 00000060 09485245

02 FC:1253 1020.00 OP

This brief contains items under the following headings as required by 37 C.F.R. §

41.37 and M.P.E.P. § 1206:

I.	Real Party In Interest
II	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments
V.	Summary of Claimed Subject Matter
VI.	Grounds of Rejection to be Reviewed on Appeal
VII.	Argument
VIII.	Claims
Appendix A	Claims Appendix

I. REAL PARTY IN INTEREST

NYCOMED AMERSHAM, PLC is the assignee of the above-captioned application, as evidenced by an assignment of the entire right, title and interest in the application recorded in the U.S. Patent and Trademark Office at reel 10899, frame 0478. Nycomed Amersham is now a subsidiary of GE Healthcare. As such, the real party in interest for this appeal is:

GE HEALTHCARE

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are a total of 8 claims pending in the application. These claims are claims 7-14 as attached hereto as Appendix A. Claims 1-6 were cancelled during prosecution.

B. Current Status of Claims

1. Claims canceled: 1-6
2. Claims withdrawn from consideration but not canceled: none
3. Claims pending: 7-14
4. Claims allowed: none
5. Claims rejected: 7-14.

C. Claims On Appeal

The claims on appeal are claims 7-14.

IV. STATUS OF AMENDMENTS

There are no outstanding or unentered amendments in the above application.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to the field of DNA manipulation. More specifically, the invention relates to the discovery that there is a problem with longer, dried oligonucleotide primers commonly used in DNA synthesis, wherein the longer primers self-anneal and lose reaction efficiency, and that the solution to the self-annealing problem lies in the use of shorter dried oligonucleotides. The invention provides methods of forming random mixtures of dried oligonucleotides which are resistant to self-annealing. The method comprises the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mers and drying the mixture.

VI. GROUNDS OF OBJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are as follows:

(a) Whether the Examiner erred as a matter of law in maintaining an obviousness rejection of claims 7-10 and 11-14 over Godiska, U.S. 5,759,804, in view of Shen, EP 0 726 310, in the face of evidence demonstrating unexpected results over the art, because Applicant's claims do not recite the unexpected results and do not contain limitations "that would suggest that such [unexpected] results were achieved," (Office Action of 7/12/04, page 5, lines 14-15).

(b) Whether claims 7-10 are indefinite under 35 U.S.C. §112, second paragraph.

(c) Whether claims 7-10 fail to comply with the written description requirement under 35 U.S.C. §112, first paragraph.

VII. ARGUMENT**A. THE REJECTION OF CLAIMS 7-14 UNDER 35 U.S.C. § 103(a) OVER GODISKA AND SHEN SHOULD BE REVERSED BECAUSE THE LAW DOES NOT REQUIRE THAT CLAIM ELEMENTS TEACH THE ACHIEVEMENT OF UNEXPECTED RESULTS OR SUGGEST THE DESIRABILITY OF AN APPLICANT'S SOLUTION TO A PROBLEM.**

The rejection of claims 7-14 under 35 USC § 103(a) over Godiska in view of Shen should be reversed because the Examiner applied an incorrect legal standard in maintaining an obviousness rejection by requiring that the claims recite "limitations... that would suggest that such [unexpected] results were achieved" (Office Action of 7/12/04 at page 5, lines 14-15), when the applicant had demonstrated unexpected results over the prior art. Moreover, the Examiner erroneously rejected the claims when she asserted that the claims did not "recite any features which would suggest the desirability" of the inventor's solution to a problem facing the art. (Office Action of 7/12/04 at page 5, lines 10-12). As will be discussed below there are no requirements that claim elements teach the achievement of unexpected results or suggest the desirability of an applicants' solution to a problem.

The present invention relates to the art of recombinant DNA synthesis and use of random primer kits to rapidly and efficiently synthesize DNA. Random primers are short segments of DNA that consist of essentially every possible combination of nucleotide bases for a given length. They are often used to carry out DNA syntheses when the sequence of a particular gene may not be known and specific primers for that gene are therefore unavailable. Workers select random primer collections of various lengths (e.g., 6-mers, 10-mers, 15-mers), but the primers themselves are random for a selected length.

Various kits containing liquid solutions of oligonucleotides were known in the prior art for practice of random priming methods. (Stratagene) While short, randomly generated nucleotide primers in solution (e.g., liquid 6-mers) were provided in these kits,

there had been a trend in the art of DNA synthesis toward using liquid solutions of longer primers in order to provide more rapid priming (e.g., Megaprime and Ready-To-Go kits). Other commercially available kits in the art provided dried primer kits which contained long primers, such as dried 15-17 mers (e.g., Rediprime, EP 298,269) or dried 48- and 22-mers (e.g., Shen, EP 0 726 310). Long, dried primers were preferred to short, dried primers because of the belief that such longer primers would provide more rapid priming than shorter primers.

The present invention relates to the discovery that long dried primers frequently bind to themselves, i.e., self-anneal or self-prime, rather than to the DNA to be synthesized. Applicant has discovered that short (6-8 mers) dried primers unexpectedly resist self-annealing and provide improvements in activity and labeling intensity compared with longer dried primers. Specifically, Examples 2 and 4 demonstrate these unexpected results by identifying a critical difference in self-priming (self-annealing) activity and labeling intensity between short dried 6-8 mers which resist self-annealing compared with longer long dried 9-mers (and above) then used in the art.

The application Examples demonstrate a critical and unexpected difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers and there is no suggestion in the art that such a difference could occur. Accordingly, the obviousness rejection under 35 U.S.C. §103(a) should be reversed because Godiska and Shen fail to teach the desirability of short primers (6-8 mers) in a dried primer system or that 6-8 mers would behave differently with respect to self-priming activity and labeling intensity than do 9-mers.

More specifically, Godiska discloses liquid 6-mers but fails to teach (1) that the selection of 6-mers to 8-mers constitutes a critical range or (2) that short primers (6-8

mers) would be desirable in a dried primer system. While Godiska discloses a random mixture of 6-mers and other ingredients, the Examiner acknowledged that Godiska does not teach a labeling composition in a dry state. Moreover, there is nothing in Godiska that teaches that the selection of 6-mers to 8-mers is important in either a liquid or dried state to reduce self-annealing.

In addition, Shen discloses dried 48-mer and 22-mer primers but fails to suggest that such dried primers should be shortened, or, alternatively any reason why the short primers of Godiska should be dried. This is because the prior art generally taught that longer primers were preferred because longer primers have higher melting temperatures and are thus more specific.

While the Examiner does not dispute the unexpected results demonstrated in the application¹, she asserts that the claims are unpatentable because the claims do not recite the unexpected results or suggest the desirability of Applicant's solution to the problem of self-annealing. This rejection should be reversed!

Evidence of unexpected results can be used to rebut an obviousness rejection. In re Chupp 816 F.2d 643, 646; 2 USPQ2D 1437, 1439 (Fed. Cir. 1987). While such evidence of unexpected results can be presented by way of Declaration, it can also be presented within the specification itself. Carter-Wallace, Inc. v. Otte, 474 F.2d 529, 176 USPQ 452 (2nd Cir. 1972). There is no requirement, however, that the claims must recite the unexpected results. See In re Merchant² (575 F.2d 865, 869, 197 USPQ 785, 788 (CCPA

¹ See Office Action of 7/12/04 at page 6, lines 20, through page 7, line 3.

² The prior art in In re Merchant disclosed a "wet" process for purifying a compound while applicant claimed a "dry" purification process resulting in unexpected improvements over the prior art. While the change from "wet" to "dry" might have seemed minor, the court stated that "the difference acquires significance, however, when it is realized that appellant's contribution to the art resides in the simplicity of his process. Id at 868.

1978)), in which the court reversed a holding of obviousness stating “we are aware of no law requiring that unexpected results relied upon for patentability be recited in the claims.”

Because the Examiner has applied an improper legal standard, that the claims recite “limitations...that would suggest that such [unexpected] results were achieved” and that the claims “recite features which would suggest the desirability” of the inventor’s solution to a problem, the rejections should be reversed.

B. THE REJECTION OF CLAIMS 7-10 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE REVERSED.

The indefiniteness rejection of claims 7-10 under 35 U.S.C. § 112, second paragraph, should be reversed because the two steps of “selecting a random mixture of oligonucleotides” and “drying the mixture” would be readily understood by a worker of ordinary skill in the art to achieve the goals of the claimed invention.

The Examiner contends that it is unclear what is meant by “selecting” a random mixture of oligonucleotides, and suggests that a worker of skill in the art could not select a mixture of random primers having self-annealing-resistant properties. The first step of “selecting a random mixture of oligonucleotides” is readily understood by those of ordinary skill in the art of DNA synthesis as simply choosing or using a random collection of oligonucleotides of a specific nucleotide length. For example, Godiska, at col. 8, lines 26-31, describes preparing a DNA probe using a denatured DNA fragment, dNTP’s, “random hexamer primers” and DNA polymerase. Hoeltke et al., (US 5,814,502, cited in Office Action of 8/8/03) describe a DNA priming reaction using a specified amount of “random primer” (col. 4, lines 15-30). A worker of ordinary skill readily appreciates that generating or obtaining random nucleotides of a specific length is the “selecting” that is performed.

To the extent that the Examiner implies that the unexpected results obtained by practice of the invention result from a selection of primers having particular sequences, this is not the case. In fact, such a selection would, by definition, not be random. Applicant's primers are random, meaning they comprise essentially all sequences for a given length. The unexpected properties result because they are short (6-8 mers) and dried.

The Examiner's rejection on the basis that it is unclear after which step the end result of the claim is achieved should be reversed because the second and final process step of the claims is clearly stated to be "drying said mixture." The steps of selecting a random mixture of oligonucleotides and then drying the mixture complete the method of forming self-annealing resistant primers. Applicant's invention is clearly directed to "a method of forming a random mixture of oligonucleotides which is resistant to self-annealing." It is just as clear that the method comprises two steps, a) selecting a random mixture of oligonucleotides which are 6 mers to 8 mers; and b) drying that mixture.

Because no evidence or rationale had been presented that one of ordinary skill would not appreciate what is and what is not covered by the claims the rejection under §112, second paragraph, should be reversed.

C. THE REJECTION OF CLAIMS 7-10 UNDER 35 U.S.C. §112, FIRST PARAGRAPH-WRITTEN DESCRIPTION, SHOULD BE REVERSED.

The rejection on the basis that the application lacks written descriptive support for the recitation of "oligonucleotides which are resistant to self-annealing" should be reversed because those of ordinary skill in the art would recognize that the dried 6-8-mer oligonucleotide mixtures were resistant to self-annealing and self-priming as demonstrated in Examples 2 and 4.

Applicant taught, and those of skill in the art recognize, that self-priming and self-annealing are the same phenomenon (see page 3, lines 12-27 of the specification where both terms are used). Moreover, the Examiner acknowledges “a reduction in the percentage of self-priming when utilizing oligonucleotide 6-mers to 8-mers versus 9-mers.” (Office Action of 7/12/04, page 7, lines 1-2). As such, a worker of ordinary skill would appreciate that the primers of the invention, which are resistant to self-priming as acknowledged by the Examiner, are resistant to self-annealing.

The rejection on the basis that “there is no disclosure which illustrates whether or not the reduction in % of self-priming is due to a selection process” (Office Action of 7/12/04 at page 8, lines 7-8) should be reversed because the unexpected results of the invention do not result from a selection of primers having particular sequences. As discussed above, and as recognized by those of ordinary skill, Applicant’s primers are random, meaning that they comprise essentially all sequences for a given length. The unexpected properties of the primers result because they are short (6-mers to 8-mers) and dried.

Applicant describes the invention throughout the disclosure and teaches the practice of the invention in a manner such that those of ordinary skill would recognize that Applicant was in possession of the invention claimed (See In re Koller, 204 USPQ 702 (CCPA 1980)). The essential goal of the written description requirement is to clearly convey that “an applicant has invented the subject matter which is claimed “ (In re Barker, 194 USPQ 470, (CCPA 1977) cited in MPEP 2163) and no reasons have been set forth why one of ordinary skill would not believe that Applicant was in possession of the originally claimed invention at the time of filing.

Because one of ordinary skill in the art would clearly conclude from the disclosure that Applicant always considered the resistance to self-annealing of the dried 6-8 mers part of her invention, the rejection of the claims based on §112, first paragraph-written description, should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.


IX. RELATED PROCEEDINGS

No related proceedings are referenced in Section II. above, or copies of decisions in related proceedings are not provided, hence no Appendix is included.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
312-474-6300

By:



Jeffrey S. Sharp
Registration No. 31,879
Attorney for Applicant

April 26, 2005



APPENDIX A

Claims Involved in the Appeal of Application Serial No: 09/485,245

7. A method of forming a random mixture of oligonucleotides which is resistant to self-annealing comprising the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mers and drying said mixture.

8. The method of claim 7 wherein the mixture is dried by freeze-drying.

9. The method of claim 7 wherein the mixture also contains at least one of: a polymerase enzyme; a supply of nucleotides for chain extension; a labeled nucleotide; a dye; a stabilizer; and a buffer.

10. The method of claim 7 wherein the random mixture of oligonucleotides is of 6-mer oligonucleotides.

11. In a method of forming a random mixture of oligonucleotides the improvement comprising the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mers and drying said mixture.

12. The method of claim 11 wherein the mixture is dried by freeze-drying.

13. The method of claim 11 wherein the mixture also contains at least one of: a polymerase enzyme; a supply of nucleotides for chain extension; a labeled nucleotide; a dye; a stabilizer; and a buffer.

14. The method of claim 11 wherein the random mixture of oligonucleotides is of 6-mer oligonucleotides.